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(82)

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Dated 8 June 2004

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1/77

Request for grant of a patent

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The Patent Office

Cardiff Road
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Gwent NP9 1RH

1. Your reference

ITT0057PV

- 9 JUN 2003

2. Patent application number
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0313250.3

1DJUN03 E813560-1 D02639
P01/7700 0.00-0313250.3

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Istituto Di Ricerche Di Biologia
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I-00040 Pomezia (Rome)
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Patents ADP number (if you know it)

7557036002

If the applicant is a corporate body, give the country/state of its incorporation

Italy

4. Title of the invention

Therapeutic Agents

5. Name of your agent (if you have one)

Dr. J. Thompson

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow
Essex CM20 2QR

Patents ADP number (if you know it)

4392742002 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country	Priority Application number (if you know it)	Date of filing (day/month/year)

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Patents Form 1/77

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Continuation sheets of this form	0
Description	28
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Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	-
Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
Any other documents (please specify)	-

11. I/We request the grant of a patent on the basis of this application.

Signature Dr. J. Thompson Date 09 June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom — Dr. J. Thompson — 01279 440172

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THERAPEUTIC AGENTS

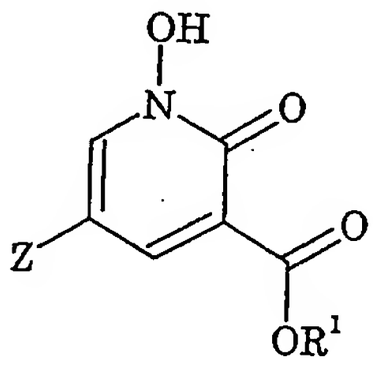
This invention relates to compounds which can act as inhibitors of viral polymerases, especially the hepatitis C virus (HCV) polymerase, to uses of such compounds and to their preparation.

The hepatitis C virus (HCV) is the major causative agent of parenterally-transmitted and sporadic non-A, non-B hepatitis (NANB-H). Some 1% of the human population of the planet is believed to be affected. Infection by the virus can result in chronic hepatitis and cirrhosis of the liver, and may lead to hepatocellular carcinoma. Currently no vaccine nor established therapy exists, although partial success has been achieved in a minority of cases by treatment with recombinant interferon-α, either alone or in combination with ribavirin. There is therefore a pressing need for new and broadly-effective therapeutics.

Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3), a helicase (NS3), and an RNA-dependent RNA polymerase (NS5B). Of these, the polymerase plays an essential role in replication of the virus and is therefore an important target in the fight against hepatitis C.

It has now been found that certain pyridinone derivatives act as inhibitors of hepatitis C virus (HCV) polymerase enzyme.

The present invention provides a compound of formula (I) below, or a pharmaceutically acceptable salt thereof:



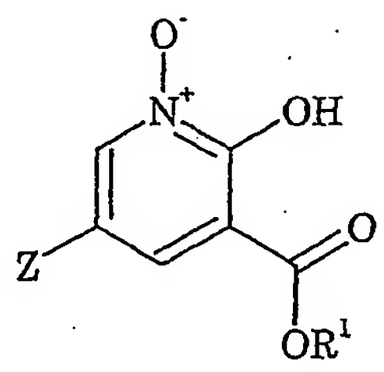
(I)

wherein

Z represents C_{2-6} alkynyl, aryl or heteroaryl, any of which groups may be optionally substituted; and

R^1 represents hydrogen, C_{1-6} alkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, di(C_{1-6})alkylamino(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy(C_{1-6})alkyl or C_{3-7} cycloalkoxycarbonyloxy(C_{1-6})alkyl.

It will be appreciated that the compound of formula (I) as depicted above may exist in equilibrium with its other tautomeric forms, including in particular the structure of formula (IA):



(IA)

wherein Z and R^1 are as defined above. It is to be understood that all tautomeric forms of the compounds of formula (I), as well as all possible mixtures thereof in any proportion, are included within the scope of the present invention.

The present invention also provides a compound of formula (I) as defined above, or a tautomer thereof, or a pharmaceutically acceptable salt thereof, for use in therapy, especially for pharmaceutical use in humans.

Typical examples of C_{1-6} alkyl groups include methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl and 1,1-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy" are to be construed accordingly.

Typical examples of C_{2-6} alkenyl groups include vinyl, allyl and dimethylallyl groups.

Typical examples of C_{2-6} alkynyl groups include ethynyl and propargyl groups.

Typical C_{3-7} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Suitable C_{3-7} heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable aryl groups include phenyl and naphthyl, especially phenyl.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

Typical aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl, phenylbutyl and naphthylmethyl.

Typical heteroaryl(C_{1-6})alkyl groups include furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

Where a compound or group is described as "optionally substituted" one or more substituents may be present. Optional substituents are not particularly limited and may, for instance, be selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} heterocycloalkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, aryloxy, aryl(C_{1-6})alkoxy, heteroaryloxy, heteroaryl(C_{1-6})alkoxy, amino, nitro, halo, hydroxy, carboxy,

formyl, cyano and trihalomethyl groups. Furthermore, optional substituents may be attached to the compounds or groups which they substitute in a variety of ways, either directly or through a connecting group of which the following are examples: amine, amide, ester, ether, thioether, sulphonamide, sulphamide, sulphoxide, urea, thiourea and urethane. As appropriate an optional substituent may itself be substituted by another substituent, the latter being connected directly to the former or through a connecting group such as those exemplified above.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Where the moiety Z in the compounds of formula (I) above represents optionally substituted C_{2-6} alkynyl, this is suitably an optionally substituted ethynyl group. A typical substituent on the C_{2-6} alkynyl group is tri(C_{1-6})alkylsilyl, especially trimethylsilyl. In this context, a typical value for the moiety Z is trimethylsilylethynyl.

Where Z represents an optionally substituted aryl or heteroaryl moiety, it may suitably be selected from phenyl, thienyl, oxazolyl, thiazolyl, furyl, isoquinolinyl, indolyl, isoxazolyl, pyrazolopyrimidinyl and pyrazinyl, any of which groups may be optionally substituted. Particular values of Z include phenyl, thienyl, thiazolyl and furyl, any of which groups may be optionally substituted. These groups may be joined to the 5-position of the pyridinone nucleus at any available position of the aryl or heteroaryl ring. However, connection at certain positions may be preferred and this is considered in some more detail below.

Preferred optional substituents on the aryl or heteroaryl group Z may be selected from a wide variety of groups. For instance, they may be simple, relatively small groups such as halogen (especially fluorine,

chlorine and bromine), hydroxy, -NO_2, -NH_2, formyl, C_{2-6} alkylcarbonyl, -CO_2H, C_{2-6} alkoxycarbonyl, C_{1-6} alkyl (especially methyl), C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, C_{1-6} alkoxy (especially methoxy), C_{1-6} alkylthio (especially methylthio), C_{1-6} alkylsulfinyl (especially methylsulfinyl) or C_{1-6} alkylsulfonyl (especially methylsulfonyl). As appropriate any of these substituents may be substituted by one or more of the others. However, in general at least one substituent is a group of formula (II):

$$-X-R^2 \qquad (II)$$

where R^2 is a generally hydrophobic moiety containing one or more, but generally at least 3, preferably 4 to 20, particularly 4 to 14, carbon atoms. Preferably, R^2 includes one or more of the following groups, any of which may, optionally, be substituted: aryl, aryl(C_{1-6})alkyl, C_{3-7} cycloalkyl, C_{1-6} alkyl (especially branched C_{1-6} alkyl), heteroaryl, heteroaryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl and C_{2-6} alkenyl. The group X is preferably selected from -NH-SO_2-, -NH-SO_2-NH-, -CH_2-SO_2-, -SO_2-NH-, -NH-CO-NH-, -NH-CS-NH-, -NH-CO-O-, -NH-CO-, -CO-NH-, -NH-CO-NH-SO_2-, -NH-CO-NH-CO-, -O-, -S-, -SO-, -SO_2-, -NH-, -CH_2-, -CH_2O- and -CH_2S-.

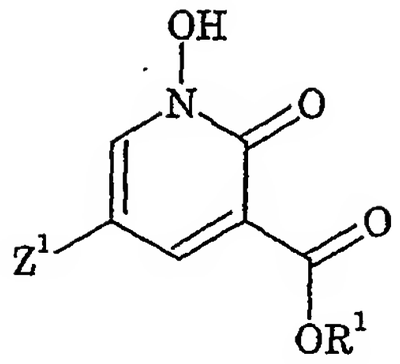
The hydrogen atom of any NH group may, optionally, be replaced by a C_{1-6} alkyl group.

Particular values of R^1 include hydrogen, methyl, ethyl, morpholinylethyl, dimethylaminoethyl, acetoxymethyl, pivaloyloxymethyl and 1-(cyclohexyloxycarbonyloxy)ethyl.

Specific values of R^1 include hydrogen, methyl and ethyl.

In one embodiment, R^1 represents hydrogen.

One illustrative sub-class of compounds in accordance with the invention is represented by formula (III) below:



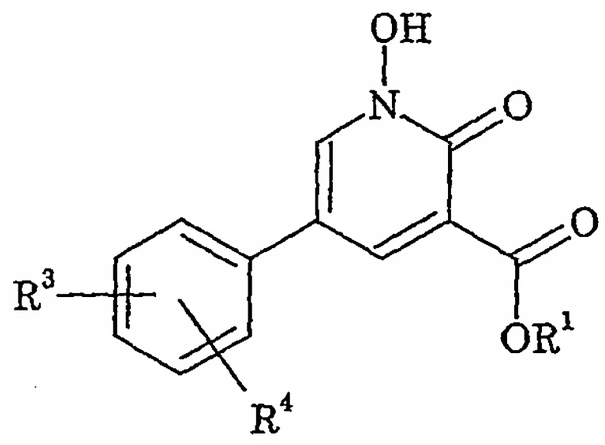
(III)

wherein

Z^1 represents optionally substituted aryl; and

R^1 is as defined above.

For instance, examples of compounds within this class are those of formula (IV):



(IV)

wherein

R^1 is as defined above; and

each of R^3 and R^4 may independently be selected from H or a substituent group.

Preferably, one of R^3 and R^4 is hydrogen, while the other is a substituent. Where a substituent is present it may be at any of the 2-, 3- or 4-positions - i.e. *ortho, meta* or *para* to the pyrimidinone nucleus. However, where a single substituent is present, substitution at the *ortho* or *meta* positions is preferred.

The substituents R^3 and R^4 may be selected from a wide variety of groups. For instance, they may be simple, relatively small groups such as

halogen (especially fluorine, chlorine and bromine), hydroxy, $-NO_2$, $-NH_2$, formyl, C_{2-6} alkylcarbonyl, $-CO_2H$, C_{2-6} alkoxycarbonyl, C_{1-6} alkyl (especially methyl), C_{2-6} alkenyl, C_{2-6} alkynyl, -CN, C_{1-6} alkoxy (especially methoxy), C_{1-6} alkylthio (especially methylthio), C_{1-6} alkylsulfinyl (especially methylsulfinyl) or C_{1-6} alkylsulfonyl (especially methylsulfonyl). As appropriate any of these substituents may be substituted by one or more of the others.

Although some such compounds are of high activity, it is generally preferable that substituent R^3 and/or R^4 include a relatively hydrophobic group R^2 which is bonded to the phenyl group through a linkage X. In this case the substituents R^3 and/or R^4 may be represented by the formula (II):

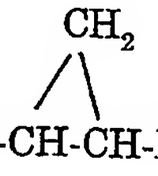
$$-X-R^2 \qquad (II)$$

where R^2 and X are as defined above.

For instance, examples of preferred classes of compound are those in which a single *ortho* or *meta* substituent is present, and that substituent is selected from the following formulae (V), (VI), (VII), (VIII) and (IX):

$$-X-(CH_2)_n-R^5 \qquad (V)$$

$$-X-CH=CH-R^5 \qquad (VI)$$



$$-X-CH-CH-R^5 \qquad (VII)$$

$$-X-(CHR^6)_p-(CH_2)_m-(CHR^6)_q-R^5 \qquad (VIII)$$

$$-X-(CH_2)_r-Y-R^5 \qquad (IX)$$

wherein

n is zero or an integer from 1 to 6, and preferably is from zero to 3, especially 0 or 1;

m is zero or an integer from 1 to 6, but preferably is 0 or 1;

each of p and q is independently 0 or 1, but preferably they are not simultaneously 1;

r is an integer from 1 to 6, preferably 1;

R^5 is an optionally substituted aryl, heteroaryl, C_{3-7} cycloalkyl, C_{3-7} heterocycloalkyl or branched C_{1-6} alkyl group;

each R^6 is independently a C_{1-6} alkyl group (especially methyl), a C_{3-7} cycloalkyl group, an optionally substituted aryl group (especially phenyl), hydroxy or hydroxy(C_{1-6})alkyl (especially hydroxymethyl), any of which may be optionally etherified, or -NH_2, optionally protonated, alkylated or derivatised as a urethane group; and

Y is selected from -O-, -S- and -NH-.

In each of the formulae (V) to (IX) the linkage X may be any of the X groups specified above.

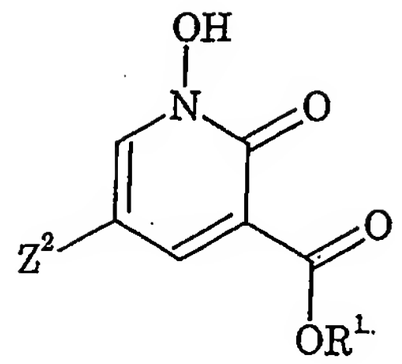
Among the groups X, the sulfonamide (-NH-SO_2-), urea (-NH-CO-NH-), urethane (-NH-CO-O-) and amide (-NH-CO-) groups are favoured. A particular value of X is -NH-CO-NH-SO_2-.

In a specific embodiment, X represents -NH-CO-NH- or -NH-CO-.

The group R^5 is preferably an aryl or heteroaryl group, of which optionally substituted phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl and thiazolyl are particularly preferred examples. Each of these may, optionally, be substituted by another optionally substituted aryl or heteroaryl group of the same or different type.

Typical compounds of formula (IV) are specifically exemplified herein as Examples 1 to 5. All those compounds have IC_{50} values no greater than 100 μM when measured in the assay described below.

Another illustrative sub-class of compounds in accordance with the invention is represented by formula (X) below:



(X)

wherein

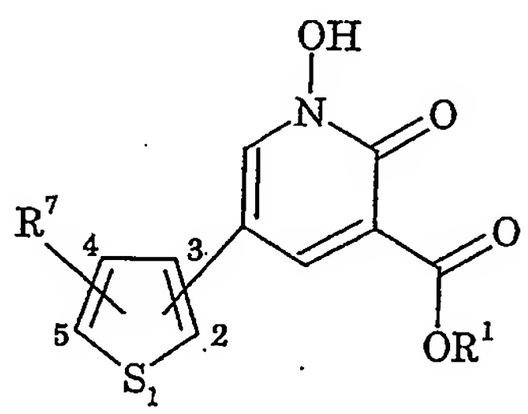
Z^2 represents optionally substituted heteroaryl; and

R^1 is as defined above.

Particular values of Z^2 include thienyl, thiazolyl and furyl, especially thienyl, any of which groups may be optionally substituted.

Preferred compounds in this sub-class are those in which the heteroaryl group Z^2 is unsubstituted, or carries a single substituent R^7, as defined *infra*.

A favoured subset of the compounds of formula (X) is represented by formula (XI) below:



(XI)

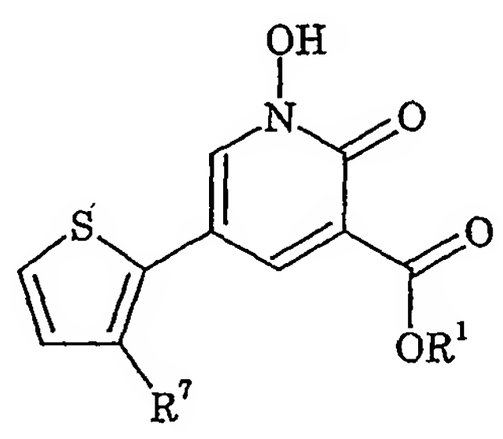
wherein

R^1 is as defined above; and

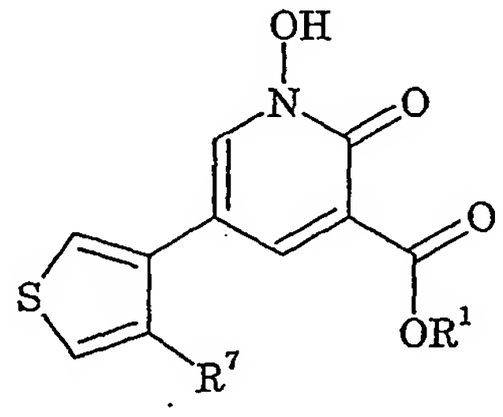
R^7 is as defined *infra*.

The pyridinone nucleus and the R^7 substituent may be at any position on the thiophene ring. However, it is preferred that when the pyridinone is at position 2 on the thiophene ring, then substituent R^7 is at

the 3-position, substitution at the 4- or 5-positions being less preferred. When the pyridinone group is at the 3-position of the thiophene ring, then R^7 is preferably at the 2- or 4-position of the thiophene ring, more preferably at the 4-position. In summary, favoured compounds in accordance with the present invention are represented by formula (XII) and (XIII) below:



(XII)



(XIII)

wherein

R^1 is as defined above; and

R^7 is as defined *infra*.

Substituent R^7 may be selected from a wide variety of groups. For instance, like substituents R^3 and R^4 discussed above it may be a simple, relatively small group such as halogen (especially fluorine, chlorine and bromine), hydroxy, $-NO_2$, $-NH_2$, formyl, C_{2-6} alkylcarbonyl, $-CO_2H$, C_{2-6} alkoxycarbonyl, C_{1-6} alkyl (especially methyl), C_{1-6} alkenyl, C_{2-6} alkynyl, -CN, C_{1-6} alkoxy (especially methoxy), C_{1-6} alkylthio (especially methylthio), C_{1-6} alkylsulfinyl (especially methylsulfinyl) or C_{1-6} alkylsulfonyl (especially methylsulfonyl). As appropriate any of these substituents may be substituted by one or more of the others.

More preferably, however, R^7 includes a relatively hydrophobic group which is bonded to the thienyl group through a linkage X. In this case, the group R^7 may be represented by the formula (II):

$$-X-R^2 \qquad (II)$$

where X and R^2 are as defined above.

Preferred X groups are amide, sulphonamide, urea and urethane linkages. A particularly preferred X group is -NH-CO-NH-SO_2-. Preferred R^2 groups are those shown in formulae (V) to (IX) already discussed above, and which include a group R^5. Advantageously, R^2 is naphthyl.

Preferred R^5 groups are aromatic groups, especially phenyl, naphthyl, thienyl, pyridyl, benzothienyl, indolyl, benzimidazolyl and oxazolyl groups. When R^5 comprises fused aromatic rings, the connection to the remainder of the R^2 group may be through any ring.

Preferred optional substituents on R^5, especially in the case where R^5 is an aryl group, include halogen (e.g. fluorine, chlorine and/or bromine), nitro (-NO_2), C_{1-6} alkyl (especially methyl), C_{1-6} alkoxy (especially methoxy), trifluoromethyl and aryl (especially phenyl).

Suitably, n is zero.

Suitably, R^5 is naphthyl.

In another aspect, the invention provides the use of a compound of formula (I) as defined above, or a tautomer thereof, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C virus in a human or animal.

A further aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I) as defined above, or a tautomer thereof, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier. The composition may be in any suitable form, depending on the intended method of administration. It may for example be in the form of a tablet, capsule or

liquid for oral administration, or of a solution or suspension for administration parenterally.

The pharmaceutical compositions optionally also include one or more other agents for the treatment of viral infections such as an antiviral agent, or an immunomodulatory agent such as α-, β- or γ-interferon.

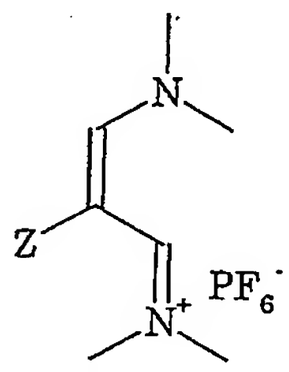
In a further aspect, the invention provides a method of inhibiting hepatitis C virus polymerase and/or of treating or preventing an illness due to hepatitis C virus, the method involving administering to a human or animal (preferably mammalian) subject suffering from the condition a therapeutically or prophylactically effective amount of the pharmaceutical composition described above or of a compound of formula (I) as defined above, or a tautomer thereof, or a pharmaceutically acceptable salt thereof. "Effective amount" means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

The dosage rate at which the compound is administered will depend on a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age of the patient, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition and the host undergoing therapy. Suitable dosage levels may be of the order of 0.02 to 5 or 10 g per day, with oral dosages two to five times higher. For instance, administration of from 10 to 50 mg of the compound per kg of body weight from one to three times per day may be in order. Appropriate values are selectable by routine testing. The compound may be administered alone or in combination with other treatments, either simultaneously or sequentially. For instance, it may be administered in combination with effective amounts of antiviral agents, immunomodulators, anti-infectives or vaccines known to those of ordinary skill in the art. It may be administered by any suitable route, including orally, intravenously, cutaneously and subcutaneously. It may be administered directly to a suitable site or in a manner in which it targets a

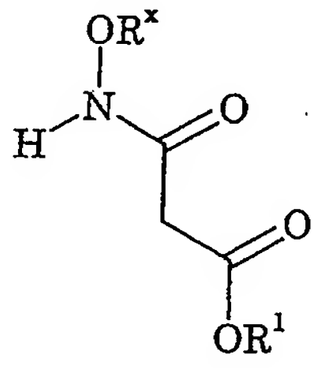
particular site, such as a certain type of cell. Suitable targeting methods are already known.

An additional aspect of the invention provides a method of preparation of a pharmaceutical composition, involving admixing at least one compound of formula (I) as defined above, or a tautomer thereof, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable adjuvants, diluents or carriers and/or with one or more other therapeutically or prophylactically active agents.

The compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula (XIV) with a compound of formula (XV):



(XIV)



(XV)

wherein Z and R^1 are as defined above, and R^x represents a hydroxy-protecting group; followed by removal of the hydroxy-protecting group R^x.

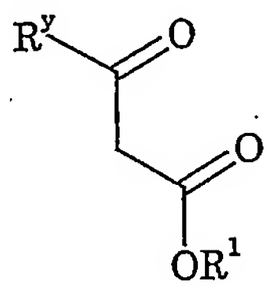
The reaction between compounds (XIV) and (XV) is conveniently accomplished at an elevated temperature in the presence of a base such as potassium *tert*-butoxide, typically in a solvent such as tetrahydrofuran.

Typical values for the hydroxy-protecting group R^x include *tert*-butyl and benzyl, in which case the hydroxy-protecting group R^x can be removed by treatment with a strong acid, e.g. hydrochloric acid, or by catalytic hydrogenation.

The intermediates of formula (XIV) above may be prepared from the corresponding compound of formula $Z\text{-}CH_2\text{-}CO_2H$ by treatment with phosphorus oxychloride and *N,N*-dimethylformamide at an elevated

temperature (e.g. 70°C); followed by treatment with hexafluorophosphoric acid in the presence of a base such as sodium hydroxide.

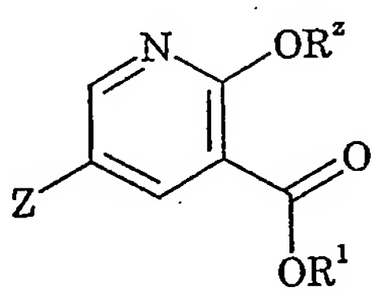
The intermediates of formula (XV) above may be prepared by reacting a compound of formula $H_2N\text{-}OR^x$ with a compound of formula (XVI):



(XVI)

wherein R^1 and R^x are as defined above, and R^y represents hydroxy or a halogen atom, e.g. chloro.

In another procedure, the compounds according to the present invention may be prepared by a process which comprises oxidizing a compound of formula (XVII):



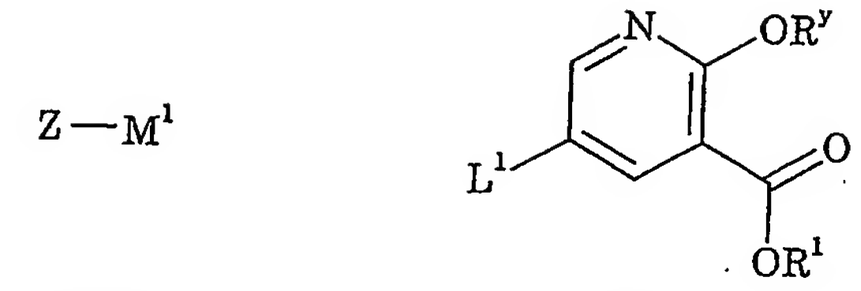
(XVII)

wherein Z and R^1 are as defined above, and R^z represents $C_{1\text{-}6}$ alkyl, e.g. methyl; followed by cleavage of the R^z moiety.

The oxidation of compound (XVII) is conveniently accomplished by treatment with a peracid, e.g. trifluoroperacetic acid.

Cleavage of the R^z moiety may conveniently be effected by treatment with a strong acid, e.g. hydrochloric acid.

The intermediates of formula (XVII) above may be prepared by reacting a compound of formula (XVIII) with a compound of formula (XIX):



(XVIII)

(XIX)

wherein Z, R^1 and R^y are as defined above, L^1 represents a suitable leaving group, and M^1 represents a boronic acid moiety $-B(OH)_2$ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol; in the presence of a transition metal catalyst.

The leaving group L^1 is typically a halogen atom, e.g. bromo.

The transition metal catalyst of use in the reaction between compounds (XVIII) and (XIX) is suitably tetrakis(triphenylphosphine)-palladium(0). The reaction is conveniently carried out at an elevated temperature in a solvent such as toluene, tetrahydrofuran, 1,4-dioxane or *N,N*-dimethylformamide, typically in the presence of potassium phosphate, sodium carbonate, cesium carbonate or copper(I) iodide.

Where they are not commercially available, the starting materials of formula (XVI), (XVIII) and (XIX) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. For example, a compound of formula (I) wherein the moiety Z is substituted by a simple, relatively small group as specified *supra* may be converted into the corresponding compound wherein Z is substituted by a group of formula (II) as defined above by means of procedures analogous to those described in many of the accompanying Examples. By way of specific example, a compound of

formula (I) wherein Z is substituted by nitro may be converted into the corresponding compound wherein Z is substituted by amino by means of catalytic hydrogenation. A compound of formula (I) wherein R^1 represents hydrogen may be converted into the corresponding compound wherein R^1 is other than hydrogen by means of conventional esterification procedures, e.g. by treatment with the appropriate alcohol of formula R^1-OH in the presence of a mineral acid such as hydrochloric acid. A compound of formula (I) wherein R^1 is other than hydrogen may be converted into the corresponding compound wherein R^1 is hydrogen by means of standard saponification techniques, e.g. by treatment with an alkaline reagent such as sodium hydroxide or lithium hydroxide.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention are potent inhibitors of HCV polymerase. The IC_{50} values in μM of these compounds can be measured in the following way.

Test for Inhibition of Hepatitis C Virus RdRp

WO 96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme. The purified enzyme was shown to possess *in vitro* RNA polymerase activity using RNA as template. The reference describes a polymerisation assay using poly(A) as a template and oligo(U) as a primer. Incorporation of tritiated UTP is quantified by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the compounds of the accompanying Examples as inhibitors of HCV RdRp.

Incorporation of radioactive UMP was measured as follows. The standard reaction (100 μl) was carried out in a buffer containing 20 mM tris/HCl pH 7.5, 5 mM $MgCl_2$, 1 mM DTT, 50 mM NaCl, 1 mM EDTA, 2OU Rnasin (Promega), 0.05% Triton X-100, 1 μCi [^{3}H]-UTP (40 Ci/mmol, NEN), 10 μM UTP and 10 μg/ml poly(A). $Oligo(U)_{12}$ (1 μg/ml, Genset) was added as a primer. The final NSSB enzyme concentration was 20 nM. After 1 h incubation at 22°C the reaction was stopped by adding 100 μl of 20% TCA and applying samples to DE81 filters. The filters were washed

thoroughly with 5% TCA containing 1M Na_2HPO_4/NaH_2PO_4, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. By carrying out the reaction in the presence of various concentrations of each test compound it was possible to determine IC_{50} values for each compound utilizing the formula:

$$\% \text{ residual activity} = 100/(1+[I]/IC_{50})^S$$

where [I] is the inhibitor concentration and "s" is the slope of the inhibition curve.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess an IC_{50} value of 100 μM or less.

EXAMPLE 1

1-Hydroxy-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid

a) 5-Bromo-2-hydroxynicotinic acid

This compound was prepared according to the procedure of Y. S. Lo (*Synthetic Communications*, 1989, 553). Bromine (0.77 eq) was added dropwise at 0°C to a stirred solution of 50% NaOH (2.4 eq) in water (1 M solution). After 5 min, 50% NaOH (3 eq) followed by solid 2-hydroxynicotinic acid (1 eq) was added to the mixture and the resulting solution was stirred at 50°C. After 20 h, a solution prepared by adding bromine (0.38 eq) to 50% NaOH (1.2 eq) in water (1 M solution) was added to the reaction mixture and stirring continued for another 24 h at 50°C. After that time the reaction mixture was cooled to 0°C and acidified to pH 2 with concentrated hydrochloric acid to allow the formation of a solid which was isolated by filtration, washed with warm water/isopropanol (3:1), then with diethyl ether and dried to afford 5-bromo-2-

hydroxynicotinic acid (87%) as an off-white solid. δ_H (400 MHz; DMSO) 8.25 (1H, d, *J* 2.7), 8.33 (1H, d, *J* 2.7), 13.84 (2H, bs); δ_C (400 MHz; DMSO) 99.45, 117.97, 142.01, 147.42, 163.22, 163.88; *m/z* (ES^-) 218-216 $(M-H)^-$.

b) Methyl 5-bromo-2-methoxynicotinate

A solution of 5-bromo-2-hydroxynicotinic acid (1 eq) and *N,N*-dimethylformamide (1 eq) in thionyl chloride (0.88 M solution) was refluxed for 2 h. Thionyl chloride was evaporated and the residue suspended in anhydrous dichloromethane (0.7 M) and anhydrous methyl alcohol (35 eq) was added dropwise. The resulting mixture was refluxed for 1 h, then evaporated *in vacuo* to obtain an oily residue which was dissolved in dry methanol and added to a stirred solution of sodium methoxide (1.3 eq) in the same solvent (1 M solution). The reaction mixture was stirred for 3 h at room temperature then neutralized by addition of a few drops of acetic acid and extracted into ethyl acetate. The organic layer was washed with a saturated solution of aqueous sodium hydrogencarbonate, brine, dried over sodium sulfate and evaporated *in vacuo*. The residue was crystallized from hot diethyl ether to afford methyl 5-bromo-2-methoxynicotinate (44%) as beige, shiny crystals. δ_H (400 MHz; $CDCl_3$) 3.89 (3H, s), 4.01 (3H, s), 8.23 (1H, d, *J* 2.5), 8.33 (1H, d, *J* 2.5); *m/z* (ES^+) 247 ($M^+ + H$).

c) Methyl 2-methoxy-5-phenylnicotinate

Methyl 5-bromo-2-methoxynicotinate (1 eq), phenylboronic acid (1.5 eq), $K_3PO_4.H_2O$ (2 eq) and tetrakis(triphenylphosphine)palladium (0.05 eq) in toluene (0.17 M solution) were placed in a Schlenk tube, purged with 2 vacuum/argon cycles and heated at reflux overnight. The cooled reaction mixture was diluted with ethyl acetate, washed with water (2 x) and brine, then dried over sodium sulfate and evaporated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate 8:1) to afford methyl 2-methoxy-5-phenylnicotinate (93%) as a

yellowish oil. δ_H (400 MHz; $CDCl_3$) 3.93 (3H, s), 4.10 (3H, s), 7.38 (1H, t, *J* 7.2), 7.46 (2H, t, *J* 7.2), 7.55 (2H, d, *J* 7.5), 8.38 (1H, d, *J* 1.9), 7.54 (1H, t, *J* 1.9); *m/z* (ES^+) 244 ($M^+ + H$).

d) Methyl 2-methoxy-5-phenylnicotinate 1-oxide

A solution of methyl 2-methoxy-5-phenylnicotinate (1 eq) in dichloromethane (0.3 M solution) was added at room temperature to a preformed solution of trifluoroperacetic acid (5 eq) and urea in the same solvent. The peracid was prepared by adding an equimolar amount of trifluoroacetic anhydride to a suspension of urea/H_2O_2 complex in dichloromethane at 0°C and stirring the resulting suspension for 10 min at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was treated again with trifluoroperacetic acid (5 eq), and after another hour it was diluted with chloroform, thoroughly washed with saturated sodium thiosulfate, dried over sodium sulfate and evaporated. The crude residue was purified by medium-pressure RP column (Lobar-C18-Merck, water/acetonitrile 1:1) affording methyl 2-methoxy-5-phenylnicotinate 1-oxide (17%) as a yellow powder. δ_H (400 MHz; DMSO) 3.97 (3H, s), 4.30 (3H, s), 7.36-7.60 (5H, m), 7.95 (1H, d, *J* 2.5), 8.62 (1H, d, *J* 2.5); *m/z* (ES^+) 260 ($M^+ + H$).

e) 1-Hydroxy-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid

The foregoing compound (1 eq) was refluxed overnight in hydrochloric acid (6 N, 0.03 M solution). The reaction mixture was allowed to cool to room temperature, diluted with water/acetonitrile (1:1) and purified by RP-HPLC on a Prep NOVAPAK (Waters) C18 Cartridge Column (7 micron, 25 x 100 mm; Flow: 10 ml/min; Gradient: A: H_2O + 0.05% TFA; B: MeCN + 0.05% TFA; 70% A isocratic for 2 min then linear to 30% A in 5 min). The title compound was obtained after lyophilization. δ_H (400 MHz; DMSO) 7.37 (1H, t, *J* 7.3), 7.46 (2H, t, *J* 7.3), 7.67 (2H, d, *J* 7.6), 8.49 (1H, d, *J* 2.6), 8.83 (1H, d, *J* 2.6), 13.00 (1H, bs), 14.15 (1H, bs);

δ_C (400 MHz; DMSO-d_6) 116.93, 119.50, 125.98, 127.84, 129.03, 133.91, 138.64, 140.01, 158.93, 164.36; *m/z* (ES^-) 230 (M-H).

EXAMPLE 2

1-Hydroxy-5-{3-[({[1-(1-naphthyl)ethyl]amino}carbonyl)amino]phenyl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid

a) *N*-[(2*Z*)-3-(Dimethylamino)-2-(3-nitrophenyl)prop-2-enylidene]-*N*-methylmethanaminium hexafluorophosphate

Two modified literature procedures were used. According to a procedure by Coppola *et al. (J. Heterocyclic Chem.*, 1974, **11**, 51) and a procedure by I. W. Davies *et al. (J. Org. Chem.*, 2000, **65**, 4571), anhydrous DMF (3.7 eq) was added dropwise to neat phosphorus oxychloride (3 eq) with intermittent cooling in order to maintain the internal temperature below 30°C. The resulting mixture was stirred for 5 minutes at room temperature, then a solution of 3-nitrophenylacetic acid (1 eq) in dry DMF (2 M solution) was added dropwise over 5 min. The yellow-orange reaction mixture was stirred at 70°C for 2 h. The cooled reaction mixture was transferred into a dropping funnel and added, concomitantly with an aqueous solution of NaOH (5 N, 47.5 eq), to a stirred solution of commercial hexafluorophosphoric acid (60% wt; 18 eq) and NaOH (5 N, 25 eq) in water (0.1 M solution), at 0°C over 40 min. A precipitate formed, which was aged for one hour, filtered, washed with water and finally dried *in vacuo* over phosphorus pentoxide to afford the title compound as a light yellow solid (63%). δ_H (400 MHz; DMSO) 2.44 (6H, s), 3.26 (6H, s), 7.72 (1H, t, *J* 8.0), 7.77-7.79 (3H, m), 8.16 (1H, s), 8.28 (1H, d, *J* 8.0); δ_C (400 MHz; DMSO) 48.61, 102.37, 123.42, 126.16, 129.57, 134.49, 138.32, 147.29, 162.85; *m/z* (ES^+) 248 ($M^+ + H$).

b) Methyl 3-(*tert*-butoxyamino)-3-oxopropanoate

To a suspension of *O-tert*-butylhydroxylamine hydrochloride (1.1 eq) and DIPEA (2.2 eq) in anhydrous THF (0.7 M solution), cooled to 0°C, was added a solution of methyl 3-chloro-3-oxopropionate (1 eq) in the same solvent (3 M solution). The resulting suspension was stirred at room temperature for 24 h. The solid was filtered off and the remaining solution was diluted with ethyl acetate and washed with hydrochloric acid (1 N). The aqueous layer was extracted again with ethyl acetate (2 x) and with chloroform (2 x). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation afforded the title compound as a colorless oil, which solidified upon standing. δ_H (400 MHz; DMSO) 1.15 (9H, s), 3.16 (2H, s), 3.62 (3H, s), 10.52 (1H, s).

c) Methyl 1-*tert*-butoxy-5-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

A solution of methyl 3-(*tert*-butoxyamino)-3-oxopropanoate (1 eq) in anhydrous THF (0.2 M) was treated with solid potassium *tert*-butoxide (1.1 eq) at 0°C. The resulting solution was stirred for 10 min at 0°C, then for 1 h at room temperature and treated with the title compound from step b (1.3 eq), which was added in one portion. The suspension thus obtained was stirred for 4 h at 45°C, then diluted with ethyl acetate and washed with hydrochloric acid (1 N, 3 x) and brine. Drying over sodium sulfate and evaporation gave the crude product, which after purification by flash chromatography (silica gel, petroleum ether/ethyl acetate 1:2, containing 1% of MeOH) afforded methyl 1-*tert*-butoxy-5-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (67%) as a light yellow solid. δ_H (400 MHz; DMSO-d_6) 1.40 (9H, s), 3.82 (3H, s), 7.74 (1H, t, *J* 8.1), 8.11 (1H, d, *J* 8.1), 8.19 (1H, d, *J* 8.1), 8.43 (1H, d, *J* 2.7), 8.45 (1H, s), 8.67 (1H, d, *J* 2.7); δ_C (400 MHz; DMSO-d_6) 29.31, 54.48, 90.51, 116.01, 122.94, 124.23, 124.36, 132.76, 134.86, 138.71, 143.79, 144.76, 150.76, 158.15, 167.51; *m/z* (ES^+) 347 ($M^+ + H$).

d) Methyl 5-(3-aminophenyl)-1-*tert*-butoxy-2-oxo-1,2-dihydropyridine-3-carboxylate

A solution of methyl 1-*tert*-butoxy-5-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate in methyl alcohol (0.36 M) was hydrogenated at atmospheric pressure over Lindlar's catalyst (20% w/w) for 5 h. Removal of the catalyst by filtration, followed by evaporation of the solvent *in vacuo*, gave methyl 5-(3-aminophenyl)-1-*tert*-butoxy-2-oxo-1,2-dihydropyridine-3-carboxylate (95%) as an off-white solid. δ_H (300 MHz; DMSO) 1.38 (9H, s), 3.80 (3H, s), 5.20 (2H, bs), 6.55 (1H, d, *J* 7.8), 6.71 (1H, d, *J* 7.8), 6.75 (1H, s), 7.09 (1H, t, *J* 7.8), 8.24 (1H, d, *J* 2.7), 8.27 (1H, d, *J* 2.7); *m/z* (ES^+) 317 ($M^+ + H$).

e) 1-Hydroxy-5-{3-[({[1-(1-naphthyl)ethyl]amino}carbonyl)amino]phenyl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid

A solution of 3-[1-hydroxy-5-(methoxycarbonyl)-6-oxo-1,6-dihydropyridin-3-yl]benzenaminium trifluoroacetate (1 eq) in anhydrous pyridine (0.1 M) was treated with 1-(1-isocyanatoethyl)naphthalene (2 eq) and the resulting solution was stirred at room temperature overnight. Pyridine was evaporated *in vacuo* and the residue re-dissolved in THF (0.1 M), treated with aqueous potassium hydroxide (1 N, 3 eq) and heated at 45°C for 2 h. The reaction mixture was cooled in an ice-bath and acidified to pH = 1 with hydrochloric acid (1 N). The resulting mixture was diluted with water/acetonitrile (1/1) and purified by RP-HPLC using a Prep NOVAPAK (Waters) C18 Cartridge Column (7 micron, 25 x 100 mm; Flow: 10 ml/min; Gradient: A: H_2O + 0.05% TFA; B: MeCN + 0.05% TFA; 60% A isocratic for 2 min then linear to 30% A in 8 min). After lyophilization the title compound (55%) was obtained as a colorless powder. δ_H (300 MHz; DMSO) 1.56 (3H, d, *J* 6.6), 5.67 (1H, m), 6.87 (1H, d, *J* 7.8), 7.20-7.24 (1H, m), 7.31-7.33 (2H, m), 7.50-7.62 (4H, m), 7.74 (1H, s), 7.85 (1H, d, *J* 7.8), 7.97 (1H, d, *J* 7.8), 8.19 (1H, d, *J* 8.4), 8.43 (1H, d, *J* 2.7), 8.55 (1H, s), 8.74

(1H, d, *J* 2.7); δ_C (300 MHz; DMSO-d_6) 22.07, 44.58, 114.84, 116.86, 117.05, 118.73, 119.64, 122.03, 123.01, 125.40, 125.52, 126.13, 127.19, 128.56, 129.45, 130.18, 133.34, 134.34, 138.49, 139.81, 140.55, 141.05, 154.19, 158.93, 164.34; *m/z* (ES^+) 444 ($M^+ + H$).

EXAMPLE 3

5-(3-{[(5-Bromothien-2-yl)carbonyl]amino}phenyl)-1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylic acid

a) Ethyl 3-[(benzyloxy)amino]-3-oxopropanoate

A suspension of *O*-benzylhydroxylamine hydrochloride (1.1 eq) and triethylamine (2.2 eq) in anhydrous THF (0.7 M solution) was treated dropwise at 0°C with a solution of ethyl 3-chloro-3-oxopropionate (1 eq) in the same solvent (3 M solution). The resulting suspension was stirred at room temperature for 24 h. The solid was filtered off and the remaining solution diluted with ethyl acetate and washed with hydrochloric acid (1 N). The aqueous layer was extracted again with ethyl acetate (2 x) and with chloroform (2 x). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation afforded ethyl 3-[(benzyloxy)amino]-3-oxopropanoate (50%) as a colorless oil, which solidified upon standing. δ_H (300 MHz; DMSO) 1.20 (3H, t, *J* 6.9), 3.12 (2H, s), 4.10 (2H, q, *J* 6.9), 4.81 (2H, s), 7.36-7.40 (5H, m).

b) Ethyl 1-(benzyloxy)-5-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

A solution of ethyl 3-[(benzyloxy)amino]-3-oxopropanoate (1 eq) in anhydrous THF (0.2 M) was treated with solid potassium *tert*-butoxide (1.1 eq) at 0°C. The resulting solution was stirred for 10 min at 0°C, then for 1 h at room temperature. The title compound from Example 2, step b (1.3 eq) was added as a solid in one portion. The resulting suspension was

stirred for 4 h at 45°C, then diluted with ethyl acetate and washed with hydrochloric acid (1 N, 3 x) and brine. Drying over sodium sulfate and evaporation gave a crude residue, which after flash chromatography purification (silica gel, petroleum ether/ethyl acetate 1:2, containing 1% of MeOH) afforded ethyl 1-(benzyloxy)-5-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (59%) as a light yellow solid. δ_H (300 MHz; DMSO-d_6) 1.33 (3H, t, *J* 7.2), 4.31 (2H, q, *J* 7.2), 5.32 (2H, s), 7.45-7.47 (3H, m), 7.59-7.61 (2H, m), 7.74 (1H, t, *J* 7.8), 8.07 (1H, d, *J* 7.4), 8.20 (1H, d, *J* 7.4), 8.41 (1H, s), 8.43 (1H, d, *J* 2.9), 8.80 (1H, d, *J* 2.9); *m/z* (ES^+) 395 ($M^+ + H$).

c) 5-(3-{[(5-Bromothien-2-yl)carbonyl]amino}phenyl)-1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylic acid

A solution of ethyl 1-(benzyloxy)-5-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (1 eq) in MeOH/THF (1:1, 0.03 M) was hydrogenated at atmospheric pressure over Lindlar's catalyst (20% w/w) for 3 h. Removal of the catalyst by filtration, followed by evaporation of the solvent *in vacuo*, gave crude ethyl 5-(3-aminophenyl)-1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate, which was dissolved in dichloromethane (0.2 M) and triethylamine (1.1 eq). The resulting mixture was added to a preformed solution of 5-bromothiophene-2-carboxylic acid (1 eq), BOP-Cl (1 eq) and triethylamine (1.1 eq) in dichloromethane (0.2 M). After stirring the reaction mixture overnight at room temperature, it was diluted with ethyl acetate, washed with hydrochloric acid (1 N) and brine, then dried over sodium sulfate and evaporated *in vacuo*. The crude residue was dissolved in tetrahydrofuran (0.3 M) and treated with aqueous potassium hydroxide (1 N, 2.2 eq) at 50°C for 1 h. The cooled reaction mixture was diluted with water/acetonitrile (1:1) and purified by RP-HPLC using a Prep NOVAPAK (Waters) C18 Cartridge Column (7 micron, 25 x 100 mm; Flow: 10 ml/min; Gradient: A: H_2O + 0.05% TFA; B: MeCN + 0.05% TFA; 60% isocratic for 2 min, linear to 50% A in 8 min,

isocratic at 50% A for 2 min then linear again to 30% A in 4 min). The title compound (20%) was obtained as an off-white powder upon freeze-drying of the appropriate fractions. δ_H (400 MHz; DMSO) 7.39 (1H, d, *J* 3.8), 7.43-7.46 (2H, m), 7.77-7.80 (1H, m), 7.87 (1H, d, *J* 3.8), 7.95 (1H, s), 8.49 (1H, d, *J* 2.6), 8.82 (1H, d, *J* 2.6), 10.37 (1H, s), 13.05 (1H, bs), 14.20 (1H, bs); *m/z* (ES^-) 433-435 (M, M-2H).

EXAMPLE 4

5-[2-({[(2-Chlorobenzyl)amino]carbonyl}amino)phenyl]-1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylic acid

a) 2-(2-Nitrophenyl)-1,3-bis(dimethylamino)trimethinium hexafluorophosphate

Following essentially the procedure described in Example 2(a), 2-(2-nitrophenyl)-1,3-bis(dimethylamino)trimethinium hexafluorophosphate (40%) was obtained as a light yellow solid. δ_H (300 MHz; DMSO) 2.42 (6H, s), 3.28 (6H, s), 7.57 (1H, d, *J* 7.2), 7.74-7.81 (4H, m), 8.10 (1H, d, *J* 7.4); *m/z* (ES^+) 248 ($M^+ + H$).

b) Methyl 1-*tert*-butoxy-5-(2-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

A solution of methyl 3-(*tert*-butoxyamino)-3-oxopropanoate (1 eq), prepared as described in Example 2(b), in anhydrous THF (0.2 M) was treated with solid potassium *tert*-butoxide (1.1 eq) at 0°C. The resulting solution was stirred for 10 min at 0°C, then for 1 h at room temperature, and finally treated with 2-(2-nitrophenyl)-1,3-bis(dimethylamino)-trimethinium hexafluorophosphate (1.3 eq) in one portion. The suspension thus obtained was stirred for 6 h at 45°C, then diluted with ethyl acetate and washed with hydrochloric acid (1 N, 3 x) and with brine. Drying over sodium sulfate and evaporation gave a crude residue which after flash

chromatography purification (silica gel, petroleum ether/ethyl acetate 1:2, containing 1% of MeOH) afforded methyl 1-*tert*-butoxy-5-(2-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (40%) as a light yellow solid. δ_H (400 MHz; DMSO-d_6) 1.34 (9H, s), 3.76 (3H, s), 7.61 (1H, dd, J_1 7.6, J_2 1.4), 7.67 (1H, dt, J_1 8.1, J_2 1.2), 7.80 (1H, dt, J_1 7.6, J_2 1.2), 7.98 (1H, d, J 2.7), 8.09 (1H, dd, J_1 8.1, J_2 1.4), 8.30 (1H, d, J 2.7); *m/z* (ES^+) 347 ($M^+ + H$).

c) 2-[1-Hydroxy-5-(methoxycarbonyl)-6-oxo-1,6-dihydropyridin-3-yl]benzenaminium trifluoroacetate

A solution of methyl 1-*tert*-butoxy-5-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate in methyl alcohol (0.05 M) was hydrogenated at atmospheric pressure over Lindlar's catalyst (20% w/w) for 3 h. Removal of the catalyst by filtration, followed by evaporation of the solvent *in vacuo*, gave the crude amine which was dissolved in TFA/water (95/5, 0.07 M) and stirred for 4 h at room temperature. Evaporation of the volatiles, co-evaporation with toluene and trituration with diethyl ether afforded 2-[1-hydroxy-5-(methoxycarbonyl)-6-oxo-1,6-dihydropyridin-3-yl]benzenaminium trifluoroacetate (62%) as an off-white solid. δ_H (300 MHz; DMSO) 3.86 (3H, s), 6.65-6.91 (2H, m), 7.03-7.18 (2H, m), 8.04 (1H, d, J 2.5), 8.55 (1H, d, J 2.5); *m/z* (ES^+) 261 (M+H).

d) 5-[2-({[(2-Chlorobenzyl)amino]carbonyl}amino)phenyl]-1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylic acid

A solution of 2-[1-hydroxy-5-(methoxycarbonyl)-6-oxo-1,6-dihydropyridin-3-yl]benzenaminium trifluoroacetate (1 eq) in anhydrous pyridine (0.1 M) was treated with 1-chloro-2-(isocyanatomethyl)benzene (2 eq) and the resulting solution was stirred at room temperature overnight. Pyridine was then evaporated *in vacuo* and the residue re-dissolved in THF (0.1 M), treated with 1 N KOH (3 eq) and heated at 45°C for 2 h. The cooled reaction mixture, after acidification to pH = 1 with 1 N HCl, was diluted with water/acetonitrile (1/1) and purified by RP-HPLC using a

Prep NOVAPAK (Waters) C18 Cartridge Column (7 micron, 25 x 100 mm; Flow: 10 ml/min; Gradient: A: H_2O + 0.05% TFA; B: MeCN + 0.05% TFA; 70% A isocratic for 2 min then linear to 40% A in 8 min). The title compound (25%) was obtained as a colorless powder after freeze-drying of the appropriate fractions. δ_H (400 MHz; DMSO) 4.29 (2H, d, *J* 5.9), 6.81 (1H, t, *J* 5.9), 7.12 (1H, t, *J* 7.6), 7.22-7.35 (5H, m), 7.41 (1H, dd, J_1 7.6, J_2 1.9), 7.79 (1H, d, *J* 7.6), 7.94 (1H, s), 8.18 (1H, d, *J* 2.5), 8.52 (1H, d, *J* 2.5), 13.02 (1H, bs), 14.25 (1H, bs); *m/z* (ES^-) 412 (M-H).

EXAMPLE 5

1-Hydroxy-5-(2-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

A suspension of methyl 1-*tert*-butoxy-5-(2-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (see Example 4) was refluxed in hydrochloric acid (6 N, 0.03 M solution) for 45 min. The reaction mixture turned first homogeneous and then a colorless solid precipitated. After being cooled to room temperature, the solid was filtered off and washed with water (5 x) and diethyl ether (3 x), and then dried *in vacuo* to afford 1-hydroxy-5-(2-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (20%). δ_H (400 MHz; DMSO) 7.64 (1H, dd, J_1 7.6, J_2 1.5), 7.69 (1H, dt, J_1 8.2, J_2 1.5), 7.82 (1H, dt, J_1 7.6, J_2 1.2), 8.13 (1H, dd, J_1 8.2, J_2 1.2), 8.18 (1H, d, *J* 2.5), 8.69 (1H, d, *J* 2.5), 13.01 (1H, bs), 13.95 (1H, bs); *m/z* (ES^-) 275 (M^+ - H).